Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Marked-up Version Showing Changes.**"

Objection to Drawings

The drawings are objected to as being informal.

Formal drawings are being provided herewith for review.

Specification

It has been requested that the specification be reviewed for any errors.

Applicant is not aware of any pending errors, and in fact corrected errors as noted in the Preliminary Amendment filed with the Specification on October 19, 2002.

Rejection of Claim 1 and 17-32 under 35 U.S.C. § 112, Second Paragraph

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claim 1 has been canceled thereby obviating the basis for this rejection.

Pending claims 17 through 32 have been prepared to obviate similar observations.

Claims 17 through 32 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. It is noted that R_1 is further defined onto itself. Applicants respectfully traverse the rejection.

R_1 is defined in pending claims as:

(i) a hydrogen atom;

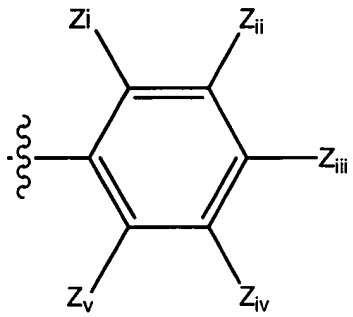
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;

(iii) a cycloalkyl of 3 to 10 carbon atoms;

(iv) an aralkyl of 7 to 12 carbon atoms;

(v) phenyl;

(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or

(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive.

It is possible that R_1 could be repeated. This does not make the claim indefinite. In fact, R_1 is clearly defined in that it can be selected from any of (i) through (viii) as moieties. Of course, only those moieties defined by (i) through (viii) are possible. This definition makes it clear what possibilities R_1 can be, even if R_1 were present more than once.

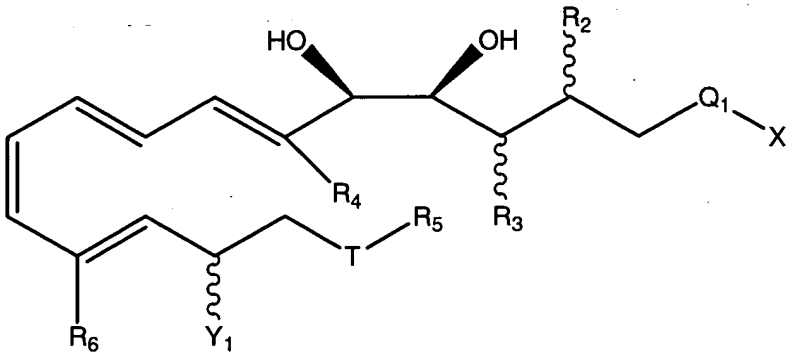
Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of Claims 1 and 17 through 32 under 35 U.S.C. § 103(a)

Claims 1 and 17 through 32 are rejected under 35 U.S.C. §103(a) as being unpatentable over "Biochemistry and Cell Biology of Phospholipase D in Human Neutrophils", Chemistry and Physics of Lipids, 80, 3 (1996) (hereinafter "Olson") in view of "Neutrophil-mediated Changes in Vascular Permeability Are Inhibited by Topical Application of Aspirin-triggered 15-epi-lipoxin A_4 and Novel Lipoxin B_4 Stable Analogues" J. Clin. Invest. 101, 819 (1998) (hereinafter "Takano").

Claim 1 has been canceled, thereby obviating this basis for rejection.

The present invention is directed to methods for the modulation of a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation; methods for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation; methods for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity; methods for treatment of PLD initiated superoxide generation or degranulation activity in a subject by the administration of an effective anti-inflammatory amount of a lipoxin analog to the subject. The lipoxin analog has the formula



wherein X is R_1, OR_1, or SR_1;

wherein R_1 is

(i) a hydrogen atom;

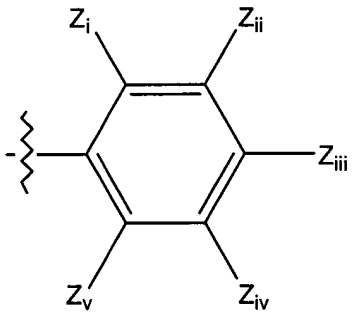
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;

(iii) a cycloalkyl of 3 to 10 carbon atoms;

(iv) an aralkyl of 7 to 12 carbon atoms;

(v) phenyl;

(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or

(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;

wherein Q_3 and Q_4 are each independently O, S or NH;

wherein one of R_2 and R_3 is a hydrogen atom and the other is

(a) H;

(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;

(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;

(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

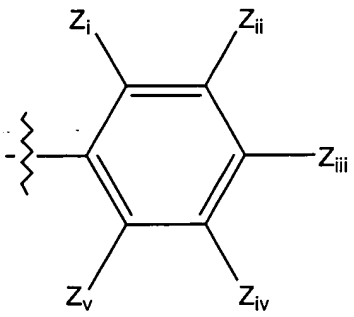
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;

(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $–NO_2$, –CN, $–C(=O)–R_1$, $–SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;

(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof.

Additionally, the present invention also relates to packaged pharmaceutical compositions which contain the lipoxin analogs and instructions to treat the afflictions described above.

Olson describes a ***biochemical pathway*** for receptor-activated phospholipase -D (PLD) in isolated neutrophils and inflammation. ***Olson fails to teach any subject matter regarding any treatment associated with such above identified afflictions***.

Olson, the primary reference, fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, as pharmaceuticals capable of modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activity.

Olson also fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, in ***packaged pharmaceuticals*** with instructions for the treatment of a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated

superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activity inflammation in a subject.

Takano, the secondary reference, fails to remedy the deficiencies of Olson. Takano teaches leukotriene B_4 (LTB_4)-induced vascular permeability change and PMN infiltration caused by the application of LTB_4 to a mouse ear. Takano fails to teach or suggest PLD-initiated PMN inflammation, let alone a method for modulating or treating a disease or condition associated with PLD initiated PMN inflammation.

Takano fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, as pharmaceuticals capable of modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityin a subject.

Takano also fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, in ***packaged pharmaceuticals*** with instructions for treatment of a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityin a subject.

Neither reference, alone or in combination teaches or suggests, provides any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, as pharmaceuticals capable of modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil

(PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityinflammation in a subject.

Neither reference, alone or in combination, teaches or suggests, provides any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, in ***packaged pharmaceuticals*** with instructions for modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityin a subject.

Therefore, claims 17-32 are in allowable form. Reconsideration and withdrawal of the pending rejection is respectfully requested.

Double Patenting

Claim 1 is rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,387,953.

Claim 1 has been canceled, thereby obviating the basis for this rejection.

Obviousness-type Double Patenting

Claims 17-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,387,953.

Upon Notice of Allowance, Applicant is willing to provide a terminal disclaimer with regard to U.S. Patent No. 6,387,953, thereby obviating the basis for this rejection.

Claims 1 and 17-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,441,951 (hereinafter '951). Applicant respectfully traverses the basis of this rejection.

U.S. Patent '951 does not teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***the lipoxin analogs***, described throughout the application, as pharmaceuticals capable of modulating a disease or condition associated with ***phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation*** or for treatment of ***PLD initiated polymorphoneutrophil (PMN) inflammation*** or for the modulation of a disease or condition associated with ***PLD initiated superoxide generation or degranulation activity*** or for treatment of ***PLD initiated superoxide generation or degranulation*** activity in a subject.

Furthermore, the '951 patent does not teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***the lipoxin analogs***, described throughout the application, in ***packaged pharmaceuticals*** with instructions for modulating a disease or condition associated with ***phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation*** or for treatment of ***PLD initiated polymorphoneutrophil (PMN) inflammation*** or for the modulation of a disease or condition associated with ***PLD initiated superoxide generation or degranulation activity*** or for treatment of ***PLD initiated superoxide generation or degranulation activity*** in a subject.

Therefore, claims 17-32 are in allowable form. Reconsideration and withdrawal of the pending rejection is respectfully requested.

Conclusion

In view of the foregoing, Applicant submits that all pending claims distinguish over all references cited by the Examiner and respectfully requests that all rejections be withdrawn. The Examiner is invited to telephone the undersigned attorney for Applicant in the event that such communication is deemed to expedite prosecution of this application.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: September 24, 2002

By: Scott D. Rothenberger

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Minneapolis, MN 55402-1498
(612) 340-8819

MARKED-UP VERSION SHOWING CHANGES

IN THE CLAIMS

23. (Amended) A method for modulating a disease or condition associated with phospholipase D (PLD) initiated superoxide generation or degranulation activity in a subject, comprising

administering to the subject an effective anti-PLD amount of a lipoxin analog having the formula

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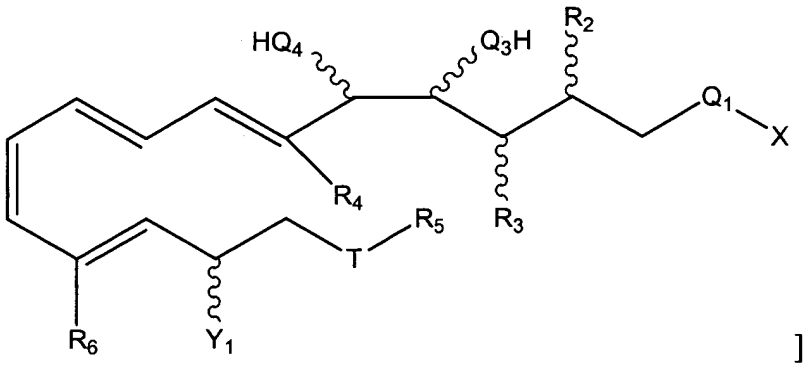

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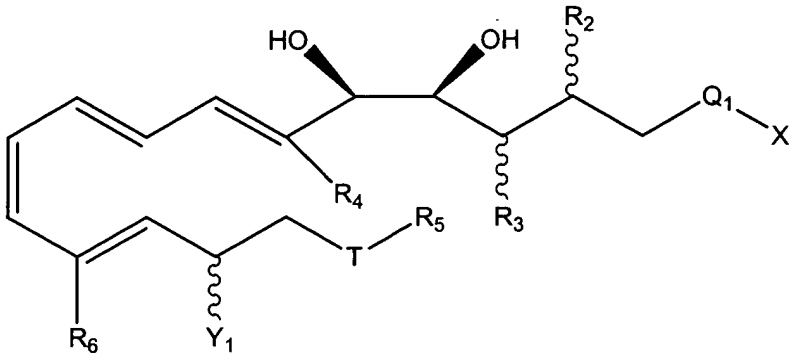


wherein X is R_1, OR_1, or SR_1;

wherein R_1 is

(i) a hydrogen atom;

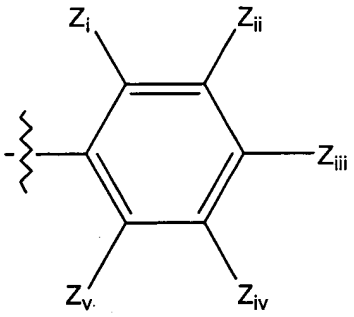
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;

(iii) a cycloalkyl of 3 to 10 carbon atoms;

(iv) an aralkyl of 7 to 12 carbon atoms;

(v) phenyl;

(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or

(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

(a) H;

(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;

(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;

(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

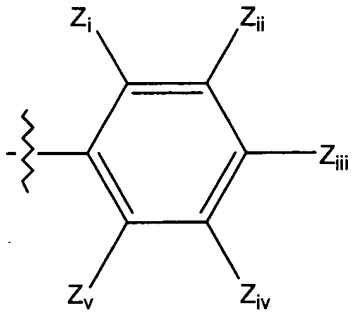
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;

(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $–NO_2$, –CN, $–C(=O)–R_1$, $–SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;

(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof, such that a disease or condition associated with PLD initiated superoxide generation or degranulation activity in a subject is modulated.

31. (Amended) A packaged pharmaceutical composition for treating a disease or condition associated with phospholipase D (PLD) initiated superoxide generation or degranulation activity in a subject, comprising:

a container holding a therapeutically effective amount of at least one lipoxin compound having the formula

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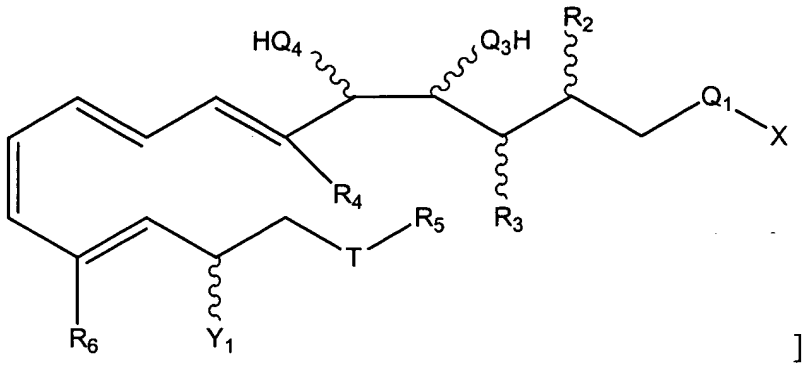

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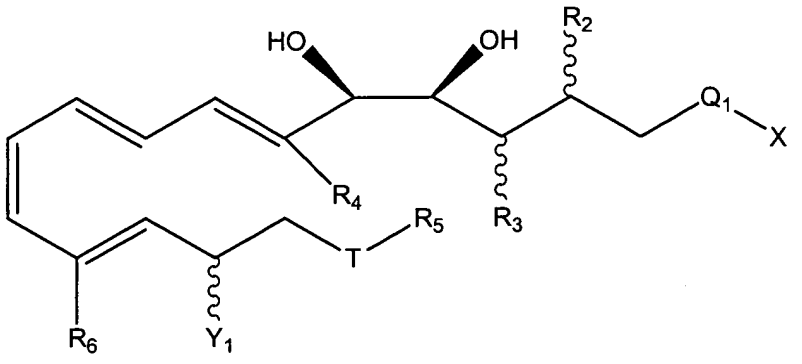


wherein X is R_1, OR_1, or SR_1;

wherein R_1 is

(i) a hydrogen atom;

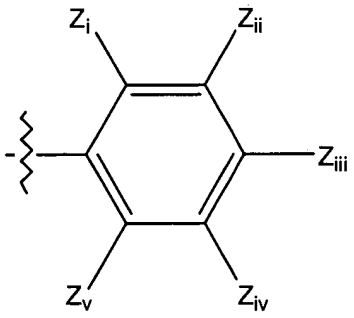
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;

(iii) a cycloalkyl of 3 to 10 carbon atoms;

(iv) an aralkyl of 7 to 12 carbon atoms;

(v) phenyl;

(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or

(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;

wherein Q_3 and Q_4 are each independently O, S or NH;

wherein one of R_2 and R_3 is a hydrogen atom and the other is

(a) H;

(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;

(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;

(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

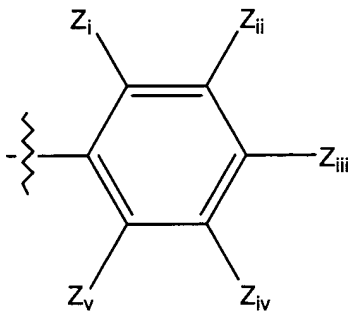
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;

(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $–NO_2$, –CN, $–C(=O)–R_1$, $–SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;

(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof; and

instructions for using said lipoxin compound for treating a disease or condition associated with PLD initiated superoxide generation or degranulation activity in the subject.